

FDA CASE STUDY

→ An infusion pump company considers risk assessment and mitigation

FREEDOM FROM UNACCEPTABLE RISK: MAKING A CASE FOR SAFETY ASSURANCE AND RISK MANAGEMENT

THIS FICTIONALIZED CASE STUDY IS THE SECOND IN AN EDUCATIONAL SERIES PUBLISHED BY THE U.S. FOOD AND DRUG ADMINISTRATION.

Henry Neyhard looked across the long, polished conference table and liked what he saw. He was meeting with Sten Laws and Rush Mooney, the first two employees of his fledgling medical device company. He had recruited them fresh out of grad school, and their intelligence and dedication to building the company were impressive. Today they were presenting to Neyhard their research on U.S. Food and Drug Administration (FDA) regulations regarding infusion pumps.

Neyhard had invented a cost-effective infusion pump that could deliver insulin at preset rates with

simple user features, increasing patient compliance and ultimately improving public health. Although the initial design focused on adult patients, Neyhard, a retired pediatrician, planned to adapt the device for pediatric diabetic care. He had every confidence in his product. His chief concern now was getting the regulatory **approval** he would need to market it.

Neyhard and his team were preparing a **premarket notification** submission for FDA, also known as a 510(k). Neyhard had started down this road before with other devices he had developed, but his lack of regulatory knowledge had been too much to overcome. This time, he was determined to be prepared.

Regulatory Background

Mooney, the company's director of product development, spoke first. "In recent years, FDA's Center for Devices and Radiological Health, or CDRH, has recognized that infusion pumps have significant safety issues. From 2005 through 2009, FDA received approximately 56,000 reports of adverse events

associated with infusion pumps, including numerous injuries and deaths. During this time period, firms conducted 87 infusion pump **recalls** to identify and resolve **safety** concerns. We want to know why some of our competitors had their products recalled so we can avoid the same mistakes." (See box, next page, for the problems reported most frequently.)

Neyhard rubbed his temples. "I knew there were recalls, but those numbers are striking."

Laws, the company's director of business development and regulatory affairs, nodded. "I know,

"From 2005 through 2009, FDA received approximately 56,000 reports of adverse events associated with infusion pumps, including numerous injuries and deaths."

and we want to make sure that doesn't happen to us. But FDA wants the same thing. The agency wants design deficiencies to be identified and corrected *before* they lead to safety problems. FDA is moving to require manufacturers of infusion pumps to include additional design and engineering information as part of their premarket submission, detailing the steps taken to mitigate **risks** at each stage of the device's **life cycle**: design, manufacture, servicing and maintenance, and use. And FDA recommends design validation testing specific to the setting where



INFUSION PUMP PROBLEMS MOST FREQUENTLY REPORTED

- **Software Defects:** Some pumps fail to activate preprogrammed alarms when problems occur, while others activate an alarm in the absence of a problem. Other software errors can lead to over- or under-infusion. In one case, a software problem called a “key bounce” caused an infusion pump to occasionally register one keystroke (e.g., a single zero, “0”) as multiple keystrokes (e.g., a double zero, “00”).
- **User Interface Issues:** Unclear instructions can lead to improper programming of medication doses or infusion rates. For example, the infusion pump screen may not make clear which unit of measurement (e.g., pounds versus kilograms) should be used to enter patient data, leading to inappropriate drug dosing.
- **Mechanical or Electrical Failures:** Device components can fail. For example, reports have included pump housings that break under routine use, premature battery failures, and sparks or pump fires. This creates risk to patients, including the potential for over- or under-administration of critical fluids.

the device is intended to be used, such as the hospital or the home, to account for real-life environmental or user interface issues.”

Neyhard was willing to do whatever it would take to ensure his product’s safety and marketability. He stood up and gathered his notes. “So let’s follow FDA’s recommendations. Put together a plan that will make it happen, and we’ll regroup a week from today.”

Safety Assurance and Risk Management for Medical Devices

Laws and Mooney remained in the conference room and exchanged looks of concern. They had a lot of ground to cover in a week, and they had neglected to share a crucial piece of information with Neyhard: they had a fundamental disagreement about how to proceed.

“Rush,” Laws said quietly. “The safety assurance case is critical. We have to do it.”

Rush knew what she was talking about. A safety case is a structured argument supported by evidence that provides a compelling, comprehensible, and valid case that a system is safe for a given application in a given environment. It is based on a philosophy of arguments pioneered by a British

philosopher, Stephen E. Toulmin, in the late 1950s. The framework has come to be used widely for the safety assurance of commercial aircraft, nuclear power plants, defense systems, and offshore drilling.

In a safety assurance case, a top-level claim (e.g., “this infusion pump is reasonably safe”) is supported by arguments that demonstrate why and how the evidence, such as performance data, supports the top-level claim. The arguments are organized in a hierarchical fashion, with each subclaim supported by evidence. A safety argument must explain the evidence that supports the overall claim of acceptable safety. (See box below.)

Mooney had some experience in medical device development and testing laboratories. He struggled now to integrate his technical knowledge with Neyhard’s commitment to patient safety and Laws’ eye toward the bottom line. “Sten, we’ve been careful. I think the company’s current risk management standard operating procedure is sufficient to meet

MAIN ELEMENTS OF AN ASSURANCE CASE

- **Claim:** Statement about a property of the system or subsystem.
- **Argument:** Links the evidence to the claim and subclaims. Arguments can be deterministic, probabilistic, or qualitative. The argument will describe the claim and identify the evidence and the reasoning to satisfy the claim.
- **Evidence:** Information that demonstrates the validity of the claim. This may include facts, analysis, research conclusions, test data, and expert opinions.

FREEDOM FROM UNACCEPTABLE RISK: MAKING A CASE FOR SAFETY ASSURANCE AND RISK MANAGEMENT CONTINUED

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FDA's expectations. We've done the risk mitigation throughout the life cycle so far, we've done the validation testing, and we know about FDA's risk management standard. The standard requires implementation of a comprehensive safety engineering system that

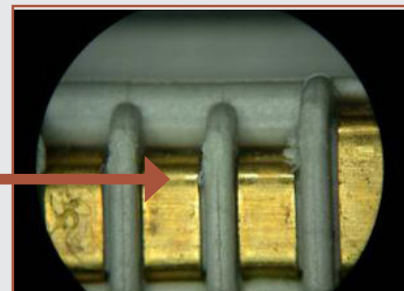
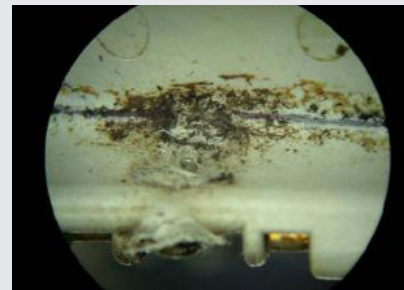
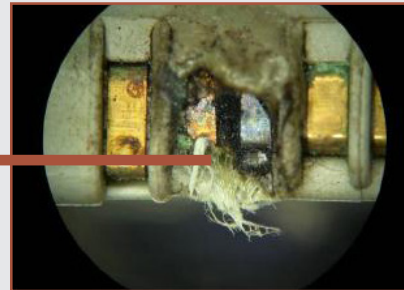
weighs risks and benefits. In fact, the standard refers to safety as 'freedom from unacceptable risk.' But the standard does not explicitly require an assurance case."

"I don't disagree," Laws responded. "But it's not enough for us to feel

confident. We need to present the evidence point by point in an organized way that adds up. The safety assurance case is a map that can get us where we want to go." The activities required by FDA's risk management standard—things like **hazard** identification and analysis,

AN INFUSION PUMP DESIGN FLAW: PUMP FIRES

One of the most serious issues with infusion pumps is reports of sparking and flames when pump modules are attached to a running unit. One company attributed this to poor user maintenance, even after ample evidence contradicted this theory. The company made design changes that reduced but did not eliminate the problem, because the changes did not address the underlying causes. FDA analysis of failed connectors revealed design deficiencies not addressed by the company. Below are photomicrographs of failed connectors taken in the CDRH mechanical engineering lab.



A FUNCTIONING CONNECTOR

THE EXPERTS RESPOND

FDA Expert

FDA recommends an assurance case report for an infusion pump premarket notification, or 510(k), submission. Neyhard’s team could incorporate a safety assurance case report in its 510(k) submission to demonstrate with evidence and confidence that the pump is safe.

In August 2010, CDRH implemented a pilot program to explore the use of an assurance case framework for 510(k) submissions for infusion devices. The assurance case is valuable to both the medical device industry and FDA. It provides the medical device sponsor a systematic framework for explaining its product claims, and it provides FDA the same framework for reviewing the safety of the device.

This complements CDRH’s robust standards program, which includes the Application of Risk Management to Medical Devices standard (ISO 14971). The medical device sponsor provides the documented outputs of risk assessment and mitigation activities and final risk/benefit analyses as supportive evidence for the arguments of the device claims. The evidence should be comprehensive and relevant to the safety of the device.

Medical Device Risk Management Expert

Mooney’s reference to safety as “freedom from unacceptable risk” expresses the relationship between safety and risk. For a novice medical device manufacturer, assuring safety would not be possible without considering risks to patient health. The safety of medical devices can be attributed directly to risk assessment and risk mitigation.

The assurance case involves the first three parts of the risk management process: 1) analyze risk, 2) evaluate risk, and 3) control risk. The fourth part identifies hazards using postmarket data of similar or predicate devices; it may provide Neyhard’s team with insight for its risk assessment and mitigation efforts.

ISO 14971 stipulates a risk management process the team can depend on to support the safety assurance case report. Mooney should use his risk management activities to complement Laws’ efforts to formulate the safety assurance case report for the 510(k) submission. He should document the results of the risk management activities and share them with Laws so she can include them in the report.

risk estimation, risk control, evidence of implementation, and risk/benefit analysis—make up a critical part of the safety assurance case. In fact, the assurance case is a comprehensive, systematic risk management report. By conducting the risk management standard activities within the structured framework of an assurance case, Laws argued, companies can assure that there are no gaps.

“I thought it would be more efficient and cost effective to avoid doing an assurance case,” said Mooney. “I thought that’s what you would want.”

“I’m all about efficiency,” answered Laws. “But in this case, it’s actually more efficient to do more. And really, how much more is it? Like you said, we’re already doing exemplary risk management. This is just a framework for providing the information. By doing the assurance case, we will meet FDA’s expectations and increase our likelihood of regulatory approval. And most importantly, it will help ensure that our pump is safe and decrease the chance of adverse events and recalls.”

Application of Risk Assessment and Mitigation

Laws won her argument with Mooney; she was able to convince him that they should do the safety case. A week after their last meeting with Neyhard, the three reconvened in the conference room.

Mooney clicked on the first slide in his presentation. “Dr. Neyhard, our risk mitigation strategy covers nine areas of safety concern: electrical, mechanical, software, hardware,

FREEDOM FROM UNACCEPTABLE RISK: MAKING A CASE FOR SAFETY ASSURANCE AND RISK MANAGEMENT CONTINUED

operational, environmental, biological/chemical, use, and others to be identified. These nine areas of concern are the results of a comprehensive risk assessment effort based on a top-down approach called Fault Tree Analysis and a bottom-up approach called Failure Modes and Effects Analysis. We also follow regulatory **guidance documents** and standards to complete our tasks. For example, we follow the IEC 60601 series for electrical safety, IEC 62366 for usability, ISO/IEC 15288 for software life cycle, and others. All evidence of our work will be documented in a risk management report, or, we could call it a safety assurance case report.”

Laws continued, “And before we submit the 510(k) application to FDA, I’ll work with Rush to formulate a safety assurance case report.”

Mooney advanced to the next slide and pointed to the center branch of a diagram (see figure, next page). “This is one of the nine areas we have worked on. It’s an electrical risk assessment to support a safety assurance case. The team followed the company’s quality management system procedures that stipulated the requirements under FDA’s risk management standard. We analyzed the pump in the context of its **intended use**. We then identified

“By doing the assurance case, we will meet FDA’s expectations and increase our likelihood of regulatory approval. And most importantly, it will help ensure that our pump is safe and decrease the chance of adverse events and recalls.”

some of the hazards and **hazardous situations** associated with electrical safety. We estimated the risk associated with electrical safety that could result in potential user burns.

“The team has proven that the device is reasonably safe from electrical hazards and hazardous situations that might cause burns. The mitigation strategies were focused on the pump designs. The pumps were designed with fuses that protected the side pumps and main pumps from short circuit conditions. The circuitries were designed according to specifications, and the fuses were tested and shown to effectively protect the pumps.

“All relevant records including design schematics, description of risk control measures, and demonstration of implementation and **effectiveness** were recorded in the verification and validation protocols and reports. The documented evidence supports an argument that the user is free from unacceptable risk of burns at present, but additional hazards need to be identified and mitigated.”

ABOUT THE CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Mission

The mission of the Center for Devices and Radiological Health (CDRH) is to protect and promote the public health. We assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee. We facilitate medical device innovation by advancing regulatory science; providing industry with predictable, consistent, transparent, and efficient regulatory pathways; and assuring consumer confidence in devices marketed in the United States.

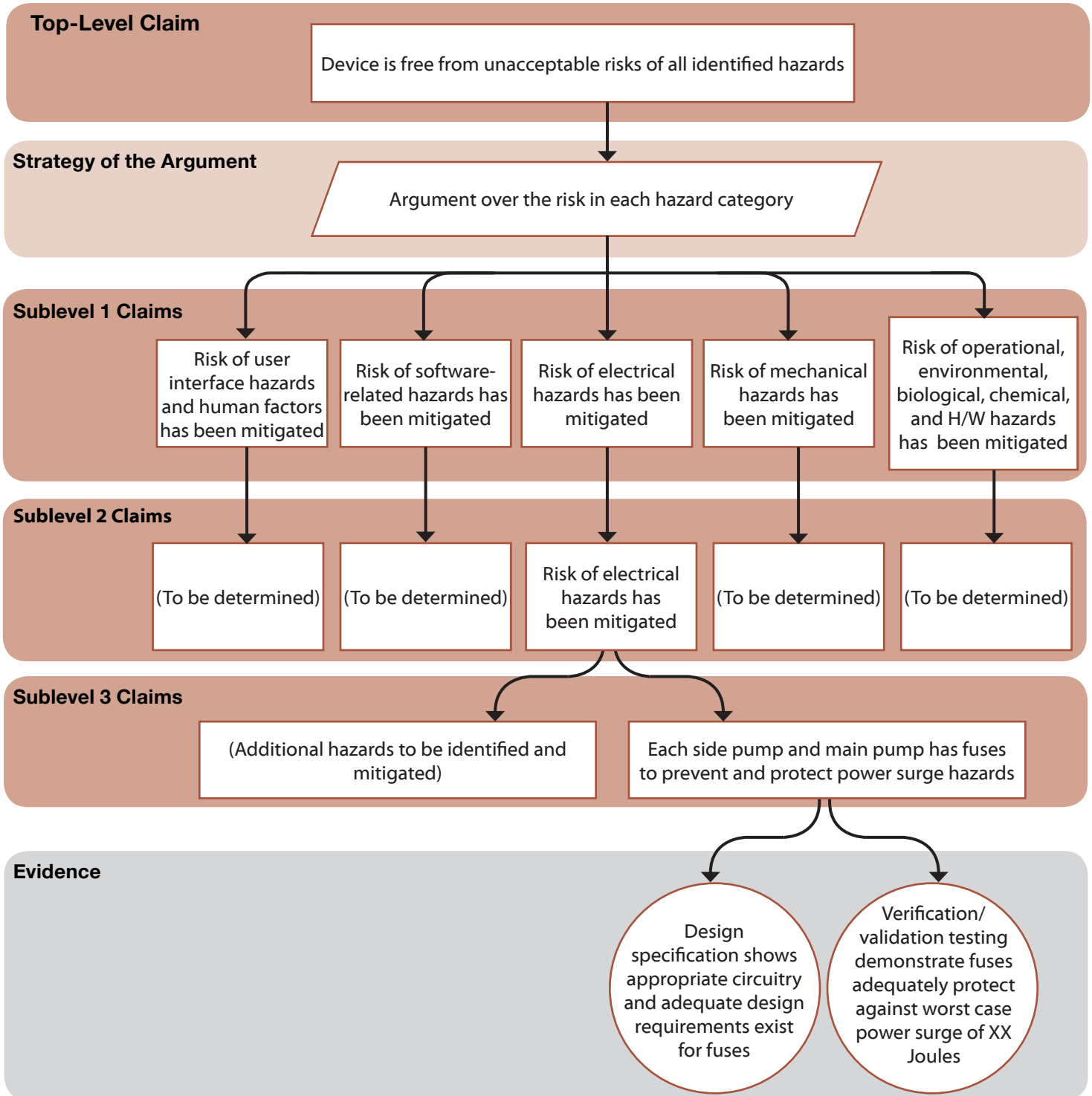
Vision

Patients in the United States have access to high-quality, safe, and effective medical devices of public health importance first in the world. The United States is the world’s leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety. U.S. postmarket surveillance quickly identifies poorly performing devices, accurately characterizes real-world performance, and facilitates device approval or clearance. Devices are legally marketed in the United States and remain safe, effective, and of high quality. Consumers, patients, their caregivers, and providers have access to understandable science-based information about medical devices and use this information to make health care decisions.

FREEDOM FROM UNACCEPTABLE RISK: MAKING A CASE FOR SAFETY ASSURANCE AND RISK MANAGEMENT CONTINUED

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➔ AN ELECTRICAL SAFETY CASE



FREEDOM FROM UNACCEPTABLE RISK: MAKING A CASE FOR SAFETY ASSURANCE AND RISK MANAGEMENT CONTINUED

“Rush,” asked Neyhard, “In the diagram, why are there no circles under some of the boxes?”

Mooney answered, “Those are the claims we are still working on. We expect to complete them in a couple of weeks. I’ll set up another meeting so you can review them.”

Conclusion

After reviewing the information about safety assurance cases and risk management, Neyhard agreed that these activities are critical to both patient safety and regulatory approval. “No one should take this lightly. I want everyone in

this company to focus not only on complying with regulations, but on showing that our devices are safe. We will design and manufacture our products as if they were intended for our own family members.”



GLOSSARY

Approval: Approval of a medical device must be obtained from the FDA by demonstrating that the device is reasonably safe and effective, and that the benefits outweigh the risks for the intended patient population before it can be put into commerce.

Critical Control Point: A point, step, or procedure in a process at which control can be applied, and a hazard can as a result be prevented, eliminated, or reduced to acceptable levels.

Critical Limit: A maximum or minimum value to which a biological, chemical, or physical parameter must be controlled at a critical control point to prevent, eliminate, or reduce to an acceptable level the occurrence of the identified safety hazard.

Effectiveness: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use will provide clinically significant results. (21 CFR Part 860.7)

Guidance Documents: Documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency’s interpretation of or policy on a regulatory issue. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Draft guidance documents are for the public to comment on and suggest changes for, but are not for implementation. (See 21 CFR Part 10.115 [b], [d], and [g])

Hazard: Potential source of harm.

Hazardous Situation: Circumstance in which people, property, or the environment is exposed to one or more hazard(s).

Intended Use/Indication For Use: “Intended use” means the general purpose of a device, or what the device does, and encompasses the indications for use. “Indications for use” describes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

FREEDOM FROM UNACCEPTABLE RISK: MAKING A CASE FOR SAFETY ASSURANCE AND RISK MANAGEMENT CONTINUED

Predicate Device: A legally marketed device to which a new device may be compared for a determination regarding substantial equivalence because the devices have the same intended use and the same technological characteristics or different technological characteristics that do not raise different questions of safety and effectiveness.

Premarket Notification—510(k) Clearance: Section 510(k) of the FD&C Act requires device manufacturers, who must register, to notify FDA of their intent to market a medical device at least 90 days in advance. This is known as premarket notification—also called PMN or 510(k). This allows FDA to determine whether the device in question is equivalent to a device already placed into Class I, Class II, or Class III requiring 510(k), or a legally marketed preamendment device. Thus, “new” devices (not in commercial distribution prior to May 28, 1976) that have not been classified can be properly identified. Specifically, medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. Such change or modification could relate to the design, material, chemical composition, energy source, manufacturing process, or intended use.

Recall: A recall of a medical device is an action taken to address a problem with the device that violates Federal law. Recalls occur when a medical device is defective, when it could be a risk to health, or when it is both defective and a risk to health.

Risk: The combination of the probability of occurrence of harm and the severity of that harm.

Risk Analysis: Systematic use of available information to identify hazards and estimate risk.

Risk Assessment: Process comprising a risk analysis and a risk evaluation.

Risk Control: Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels.

Risk Estimation: Process used to assign values to the probability of occurrence of harm and the severity of that harm.

Risk Evaluation: Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk.

Risk Management: Systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk.

Safety: There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use outweigh any probable risks. (21 CFR Part 860.7)

Safety Case or Safety Assurance Case: A structured argument supported by a body of evidence that provides a compelling, comprehensive, and valid case that a system is safe for a given application in a given environment.

Substantial Equivalence: As part of the 510(k) process, FDA may issue an order of substantial equivalence if it determines that a new medical device is as safe and effective as a similar device already being legally marketed, called the predicate device.

Total Product Life Cycle: This encompasses all phases in the life of a medical device, from the initial conception to final decommissioning and disposal.

FREEDOM FROM UNACCEPTABLE RISK: MAKING A CASE FOR SAFETY ASSURANCE AND RISK MANAGEMENT CONTINUED

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STUDENT ACTIVITIES

BEFORE CLASS

I. Review the following materials:

1. Using External Infusion Pumps Safety: FDA Patient Safety News, Show #100, July 2010
<http://www.accessdata.fda.gov/psn/printer.cfm?id=1329>
2. Infusing Patients Safely: Priority Issues From the AAMI/FDA Infusion Device Summit
http://www.aami.org/publications/summits/AAMI_FDA_Summit_Report.pdf
3. Code of Federal Regulations, Title 21, Parts 860, 807, and 820
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm>
4. Application of Risk Management to Medical Devices Standard (ISO 14971; to be provided)

II. Answer the following questions:

1. What is an infusion pump?
2. List the eight categories of hazards suggested by FDA.
3. List three hazards in each category.
4. What are the definitions of the following terms according to ISO 14971?
 - Safety
 - Risk
 - Harm
 - Hazard
 - Hazardous situation
5. What are the supportive regulatory requirements to do a safety assurance case report?

III. References

Note: Draft guidances are subject to change and are not for implementation.

1. U.S. Food and Drug Administration: Factors To Consider When Making Benefit-Risk Determination in Medical Device Premarket Approval and De Novo Classification, March 28, 2012
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>
2. U.S. Food and Drug Administration: Infusion Pump Improvement Initiative, April 2010
<http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/UCM206189.pdf>
3. Total Product Life Cycle: Infusion Pump—Premarket Notification [510(k)] Submissions Draft Guidance, April 23, 2010
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM209337.pdf>

IN CLASS

I. Questions for small group discussion

1. What are the differences between risk assessment and risk management?
2. What are the steps to do a comprehensive risk assessment?
3. How do you build a comprehensive risk management system?

FREEDOM FROM UNACCEPTABLE RISK: MAKING A CASE FOR SAFETY ASSURANCE AND RISK MANAGEMENT CONTINUED

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AFTER CLASS

I. Team project

1. Review the following two video clips from FDA Patient Safety News:
 - a. Safety Information on Alaris SE Infusion Pumps, Show #57, November 2006
<http://www.accessdata.fda.gov/psn/printer.cfm?id=471>
 - b. Baxter Infusion Pumps Recalled Because of Service Error, Show #68, October 2007
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=563>
2. Select one of the “to be determined” sublevel 2 claims from the safety case diagram on page 6 and collect publicly available information and data to formulate a risk assessment that follows the process discussed in class. Complete and discuss the short circuit claim as follows:
 - a. Claim: Power surge hazards are mitigated.
 - b. Definition: Power surge may refer to Voltage Spike, Current Spike, or Transferred Energy Spikes.
 - c. Subclaim 1: Power surge hazards are prevented.
 - d. Evidence: to be developed.
 - e. Subclaim 2: Power surge hazards are detected.
 - f. Evidence: to be developed.
 - g. Subclaim 3: Power surge hazards are mitigated.
 - h. Subclaim 3.1: Fuses are implemented to mitigate power surge hazards.
 - i. Evidence: Adequate design requirements exist for fuses.
 - j. Evidence: V/V testing demonstrate fuses adequately protect against worst case power surge of X Joules.
3. Present your risk management results in a safety assurance case report format.